REMARKS

I. Status of the Claims

Claims 1-31 were filed with the application. Claims 2, 3, 5-8 and 10-31 have been withdrawn from consideration. Thus, claims 1, 4 and 9 are under consideration and stand rejected under 35 U.S.C. §112, first paragraph (enablement). The specific grounds for rejection, and applicants' response thereto, are set out in detail below.

II. Rejection Under 35 U.S.C. §112, First Paragraph (Enablement)

Claims 1, 4 and 9 remain rejected for alleged lack of enablement. As explained below, applicants again traverse.

The rejection seems to have two aspects. First, there is a question regarding the ability to extrapolate from the acknowledged role of MEF2C in hypertrophic signaling to other MEF2 isoforms, *i.e.*, MEF2A, MEF2B and MEF2D. Second, the examiner argues that even given the proven role of MEF2C in hypertrophy, the specification provides insufficient evidence regarding efficacy. Applicants believe that the extrapolation from MEF2C to other isoforms is indeed warranted. Moreover, applicants submit that simply alleging unpredictability cannot shift the burden to applicants to provide clinical evidence of efficacy.

Applicants attach the recently published (on-line) paper by Xu *et al.* (2006) (attached). In this paper, the authors report that MEF2A behaves much as does MEF2C in terms of sarcomeric disorganization, focal elongation, altered gene expression, extracellular matrix remodelling, and ion handling. Thus, there is indeed evidence to indicate that MEF2A, like MEF2C, is involved in hypertrophic signaling. Moreover, other evidence exists indicating that MEF2A and MEF2D form a heterodimer, further suggesting a common role for these two proteins. Mora & Pessin

(2000) (attached). Moreover, there are additional studies indicating that MEF2A, MEF2C and MEF2D have similar functions with respect to interactions with MASH1 and E12. Black *et al.* (1996) (attached). Thus, to suggest that there is no basis in the literature for extrapolating from MEF2C to other isoforms of MEF2 simply is not true.

Turning to the issue of proof, applicants are confused. The examiner argues at page 4 that "the Examiner has not required any 'experimental evidence' in particular in humans or any other animal model ...." Yet on page 8, it is stated that applicants' specification needs to "provide the artisan with specific treatment regimens that achieve a therapeutic effect *in vivo* or *ex vivo*." So, which is true – are such experiments deemed required or not?

The real issue is whether the *Wands* factors mitigate in favor or against enablement. As the examiner has pointed out, there is complexity associated with hypertrophic gene regulation. Indeed, this is the only substantive argument against enablement (the other being the absence of data). However, the present invention involves the unraveling of this regulation, namely, that demonstrate MEF2 is involved in activation of hypertrophic signaling in the heart. Mice were created using a transgene in which three tandem copies of the MEF2 site from the desmin gene were inserted upstream of a heat shock protein promoter (hsp-68). Expression from this construct is downregulated to levels that are undetectable in adult animals. However, the hypertrophic signaling agents calcineurin and CAMKIV dramatically upregulated expression, indicating that MEF2 was involved in the activation of the hypertrophic response. Applicants proposal, then, was simply to block MEF2 activity as a way of blocking hypertrophic gene expression. This is what needs to be enabled.

The examiner also argues against enablement at the level of ***how***. For example, it is argued that "no starting materials to practice the claimed invention" are provided. This is not

true. Pages 23-30 provide a detailed explanation of ***how*** one can achieve inhibition of MEF2 signaling:

> Thus, in a particular embodiment of the present invention, there are provided methods for the treatment of cardiac hypertrophy. These methods exploit the inventors' observation, described in detail below, that MEF2 appears to up-regulate the expression of genes involved in the hypertrophic response. At its most basic, this embodiment will function by reducing the *in vivo* activity of MEF2 in individuals suspected of having undergone a hypertrophic response, currently undergoing a hypertrophic response, or in danger of cardiac hypertrophy. This may be accomplished by one of several different mechanisms. First, one may block the expression of the MEF2 protein. Second, one may directly block the function of the MEF2 protein by providing an agent that binds to or inactivates the MEF2 protein. And third, one may indirectly block the effect of MEF2 by interfering with one or more targets of MEF2.

Specification at page 23. The text goes on to describe a variety of materials that can be used to implement each of these embodiments, and how they can be administered. For example, page 24 of the specification states that "[t]he therapeutic compositions of the present invention may be administered in a manner similar to the administration of current treatments for heart conditions, such as aspirin, nitrates and beta blockers." Agents such as antisense polynucleotides, ribozymes, organochemical compositions, antibodies that block an active site or binding site on MEF2, or molecules that mimic an MEF2 target are all described. Thus, it is untrue that the specification fails to provide such information. Rather, it appears to simply be a matter of the examiner not believing that these materials could be used in this fashion without undue experimentation. However, this is not the standard by which enablement can be rejected.

In sum, the examiner has offered little other than the alleged complexity of the MEF2 signaling pathway to support the view that undue experimentation is required. While the examiner has acknowledged the *Wands* factors, little or no ***evidence*** has been provided on these factors, with the examiner's personal views filling in the balance of the argument. It is therefore

applicants' position that the examiner has failed to shift the burden to applicants to defend their presumptively enabling disclosure. *In re Marzocchi*, 439 F.2d 220, 224, 169 USPQ 367, 370 (CCPA 1971).

III. Conclusion

In light of the foregoing, applicants respectfully submit that all claims are in condition for allowance, and an early notification to that effect is earnestly solicited. Should Examiner Woitach have any questions regarding this response, she is invited to contact the undersigned attorney at (512) 536-3184 with any questions, comments or suggestions relating to the referenced patent application.

Respectfully submitted,

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